REMARKS

Claims 1-8, 22-21, and 23 are pending and stand rejected. Claims 9, 10, and 22 were withdrawn by the Examiner in view of the Restriction Requirement and have been cancelled without prejudice herein by Applicants, and may be pursued in a divisional application.

Applicants acknowledge the Examiner's objection to claim 1. Applicants have amended the claim to obviate this objection.

Applicants acknowledge the Examiner's rejection of claims 1-8, 11, 12, 21, and 23, under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants have amended or cancelled the subject claims to obviate this objection.

Applicants acknowledge the Examiner's rejection of claims 1-4, 6-8, 11, 12, and 21, under 35 U.S.C. § 102 (b), as being allegedly anticipated in view of Biesalski (US 5,556,611). Applicants have amended the independent claims and have provided rebuttal arguments to obviate this rejection.

Claim Objection

The Examiner objected to claim 1 in view of the inadvertent recitation of "ciliated e epithelial ... ." Applicants have amended the claim to recite "ciliated e epithelial ..." to obviate this objection, and therefore respectfully request withdrawal of this rejection.

Claim Rejections-35 U.S.C. § 112

The Examiner rejected claims 1-8, 11, 12, 21, and 23, under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in view of: (**a**) recitation of "in part" (claims 1 and 11 and dependent claims 2-8, 12, and 21); (**b**) mere recitation of a "use" (claims 13-20 and 23).

Applicants have amended or deleted the claims to obviate these rejections.

Specifically, with respect to **(a)**, Applicants have deleted the phase "in part" from independent claims 1 and 11.

With respect to **(b)**, Applicants have deleted the "use" claims 13-20 and 23, as the subject matter thereof is redundant with that of claims 1-11 and 21.

Applicants, therefore, respectfully request withdrawal of the Examiner's indefiniteness rejection (and related § 101 rejection) in view of Applicants' amendments.

Claim Rejections-35 U.S.C. § 102

The Examiner rejected claims 1-4, 6-8, 11, 12, and 21, under 35 U.S.C. § 102 (b), as being allegedly anticipated in view of Biesalski (US 5,556,611).

Specifically, the Examiner states that Biesalski teaches use of a composition (aerosol formulation) of retinoic acid (0.01-50% by weight) for topical treatment of mucosal disease, including functional impairments in the mucous membranes (respiratory epithelium and epithelia of nose-throat cavity), for treating reduced activity of ciliated epithelium and disturbances of the mucous membranes of the respiratory tract, and for treating acute and chronic bronchitis, acute and chronic functional disturbances due to impairment of tracheobronchial epithelium and broncoplumonary dysplasia.

Biesalski. The context of Biesalski is treatment of vitamin A deficiency, and is aimed at solving the side-effect problems associated with systemic administration in the prior art (see Background of Biesalski, columns 1 and 2). To this end, Biesalski teaches topical administration of retinoic acid/retinol by aerosol delivery to mucous membranes to avoid systemic side effects. Biesalski does <u>not</u> teach or suggest any delivery method beyond aerosol inhalant (spays and inhalants; "the finely distributed minute active substance particles of the aerosol reach the place of

action ..." (column 3, lines 1-14)). Biesalski does not teach or suggest depot packing, gels, etc. Not surprisingly, therefore, the claims of Biesalski are limited to the use of an "aerosol inhalant." Additionally, while Biesalski mentions "functional impairments" (column 10, lines 24-30), "cellular differentiation disturbances" (column 10, lines 31-37; claim 3), "reduced activity," and "functional anomalies, diseases and pathological changes in the mucous membranes" (e.g., Biesalski, claim 2), the scope of Biesalski is limited to mucosal diseases (see Abstract, Background, and Specification), and adjuvant therapy (*e.g.*, cancer) (e.g., Biesalski, claim 4). There is, for example, no teaching or suggestion that such therapy could be used in a surgical context or in any other context aside from disease related functional impairments and pathological changes, and in adjuvant therapy. Moreover, surgery-related damage or impairment is not even mentioned or represented in the publications and references listed in Biesalski, where all references cited are related to Vitamin A deficiency.

The teachings of Biesalski, therefore, are limited to the use of an "aerosol inhalant" for treating disease-related (*i.e.*, Vitamin A deficiency-related) functional impairments and pathological changes, and to some extent in adjuvant therapy (*e.g.*, cancer).

Relevant Law:

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on the Examiner to

identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

Applicants have amended independent claims 1 and 11 to recite "comprising topical administration of a non-aerosol depot formulation of a therapeutically effective amount of composition comprising vitamin A to a damaged ciliated epithelial structure,...wherein treating of the damaged ciliated epithelial structure is achieved." Support for the amendments is found throughout the originally-filed specification, which teaches, *inter alia*, non-aerosol administration of topical depot formulations (*e.g.*, page 8, line 8 through page 10, line 4; see also examples using gel formulations as a topical depot formulation). Recitation of "a non-aerosol depot formulation" distinguishes the presently claimed subject matter from that of Biesalski, which is strictly limited to the use of aerosolized inhalants as summarized above.

Applicants, therefore, respectfully request withdrawal of the Examiner's anticipation rejection, based on Biesalski, with respect to presently amended claims 1-4, 6-8, 11, 12, and 21. Biesalski neither anticipates, nor renders obvious the presently claimed subject matter.

Claim Rejections-35 U.S.C. § 103

The Examiner rejected claim 5, under 35 U.S.C. § 103 (a), as being allegedly obvious in view of Biesalski (US 5,556,611).

Specifically, the Examiner states that Biesalski teaches use of a composition (aerosol

formulation) of retinoic acid (0.01-50% by weight) for topical treatment of mucosal disease, including functional impairments in the mucous membranes (respiratory epithelium and epithelia of nose-throat cavity), for treating reduced activity of ciliated epithelium and disturbances of the mucous membranes of the respiratory tract, and for treating acute and chronic bronchitis, acute and chronic functional disturbances due to impairment of tracheobronchial epithelium and broncoplumonary dysplasia. Additionally, the Examiner urges that while Biesalski do not expressly teach that the surgical intervention is the cause of the damaged ciliated epithelial structure, it would have obvious to one of ordinary skill in the art to employ retinoic acid preparation taught by Biesalski for the treatment of damaged ciliated epithelial structure regardless of cause because Biesalski teach that the retinoic acid preparation is effective for the treatment of impaired epithelium, and that one would have been motivated to employ the aerosol of Biesalski to treat any symptom or condition including surgery with a reasonable expectation of success.

Applicants respectfully traverse this rejection, because no *prima facie* case of obviousness can be supported, based on Biesalski.

APPLICABLE LAW. Under KSR v. Teleflex, application of the TSM test is valid provided that such application does not require an overly rigid or explicit application of the asserted prior art. Accordingly, as already stated in the record, and in keeping with KSR, to establish a *prima facie* case of obviousness there must be: (i) a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art (POSITA), to modify the reference or to combine reference teachings; (ii) a reasonable expectation of success; and (iii) the prior art reference(s) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and knowledge generally available to

POSITA, and not based on Applicant's disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); and see MPEP §§ 2143-2143.03). Therefore, to support a conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. Moreover, there can be no reasonable expectation of success where the art, alone or in combination, *teaches away* from the invention.

Applicants respectfully traverse the Examiner's obviousness rejection, based on the fact that no *prima facie* case of obviousness is supportable in view of the asserted references alone or in combination, because **(a)** there is no suggestion or motivation embodied in the asserted art alone or in combination, even in view of knowledge generally available to one of ordinary skill in the art, to arrive at Applicants' invention, and **(b)** even if there were, there is no reasonable expectation of success based thereon where the references fundamentally *teach away* from the present invention, and **(c)** the references do not, in fact, teach all the claim limitations, and further teach elements that would preclude provision of the presently claimed subject matter.

First, with respect to (a) and as described above, and contrary to the Examiner's urging, Biesalski is absolutely silent on surgery-related damage, and the word "surgery" or "surgical" is conspicuously absent from the specification of Biesalski, or any references or publications cited or discussed in Biesalski. Contrary to the Examiner's urging, there is absolutely no teaching that treatment of disease-related (*i.e.*, Vitamin A deficiency-related) mucosal damage or impairment is applicable to the surgical-related damage or impairment. This is not surprising, since the underlying mechanisms would be expected to be fundamentally different in at least some significant respects (*e.g.*, the effects of Vitamin A deficiency are typically known in the art to be

manifested over a protracted time period, and implicate unique metabolic attributes specifically related to Vitamin A deficiency). The Examiner has given no support whatsoever for the assertion that that treatment of disease-related (*i.e.*, Vitamin A deficiency-related) mucosal damage or impairment is applicable to the surgical-related damage or impairment. Applicants respectfully submit that if the Examiner is relying on "common knowledge" or "taking official notice," with regard to the statement that "because Biesalski teach that the retinoic acid preparation is effective for the treatment of impaired epithelium, and that one would have been motivated to employ the aerosol of Biesalski to treat any symptom or condition including surgery with a reasonable expectation of success" then the Examiner must provide documentary evidence if the rejection is to be maintained. *See* 37 C.F.R. §1.104(c)(2); MPEP 2144.03. Applicants further submit that if the Examiner is relying on personal knowledge to support the finding of what is known in the art, the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. *See* 37 C.F.R. §1.104(d)(2).

Second, with respect to (b) and (c), and even if, *arguendo*, the Examiner's urging with respect to the alleged motivation to apply Biesalski aerosolized inhalants to the surgical setting was supportable, Applicants have amended independent claims 1 and 11 to recite "comprising topical administration of a non-aerosol depot formulation of a therapeutically effective amount of composition comprising vitamin A to a damaged ciliated epithelial structure,...wherein treating of the damaged ciliated epithelial structure is-achieved." As discussed above, recitation of "a non-aerosol depot formulation" distinguishes the presently claimed subject matter from that of Biesalski, which is strictly limited to the use of aerosolized inhalants in non-surgical settings as summarized above.

Significantly, Biesalski's use of "finely distributed minute active substance particles" was intended to avoid the side effects of prior art systemic administration protocols (see, *e.g.*,

Background of Biesalski). As recognized in the art, administration of finely distributed minute aerosolized particles is not a form of depot administration, and would not be expected to provide a time-release or extended release of Vitamin A. Indeed, this is the premise of Biesalski's use of finely distributed minute aerosolized particles. Therefore, in this sense, Biesalski fundamentally *teaches away* from the present depot form of administration. Additionally, with application of the sprays of Biesalski, the mucosal epithelium would not be covered (other than transiently) as would be the case for the presently claimed depot formulation (as), and therefore represents a fundamentally different mucosal surface (*i.e.*, exposed vs. depot agent-covered mucosal epithelium). Therefore, not only is the presently claimed depot administration method fundamentally different in terms of the effective time-of-release aspect, but the treatment surface (covered vs. uncovered) is different, and it would not have been predictable that one could achieve efficacy with a vitamin A depot agent application without incurring unwanted side-effects. Moreover, in the face of the acute knowledge of unwanted side effects relating to systemic delivery, one of skill in the art would not have been motivated to avoid systemic delivery by using relatively long-acting depot agents as presently claimed.

Applicants, therefore, respectfully request withdrawal of the Examiner's obviousness rejection based on Biesalski et al., which does not teach, suggest or otherwise motivate the use of Applicants' presently claimed methods "comprising topical administration of a non-aerosol depot formulation of a therapeutically effective amount of composition comprising vitamin A to a damaged ciliated epithelial structure,...wherein treating of the damaged ciliated epithelial structure is-achieved."

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request entry of the present Amendment and allowance of the amended claim set provided herein. The Examiner is encouraged to phone Applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

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